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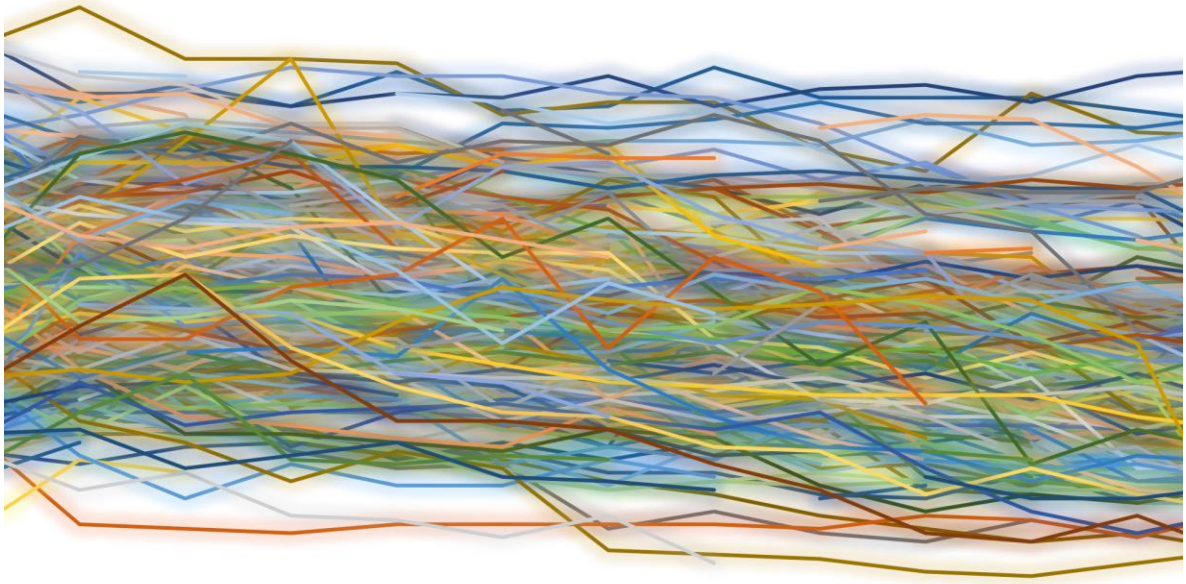

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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I dedicate this work to my wonderful wife Tiia, and to my precious children Anni, Tilia and Linnea.

ABSTRACT

Background: Social anxiety disorder (SAD) is a common mental disorder, causing considerable distress and functional disability for affected individuals and places a significant economic burden on society. However, few receive treatment due to several barriers such as low treatment availability, stigma and fear. The effectiveness of cognitive behavioural therapy (CBT) is well established, and recent innovations in e-health such as internet-based CBT (ICBT) may significantly increase access to effective care. Several trials have demonstrated that ICBT is both efficacious and cost-effective. However, before disseminating ICBT into the mental health care system, it is essential to evaluate its clinical effectiveness to study whether it works as expected when delivered as routine care in a naturalistic setting.

Aims: The aims of this doctoral project were to evaluate the clinical effectiveness of ICBT in the treatment of SAD, to assess its non-inferiority against the standard treatment and to identify outcome predictors.

Methods: Study I (N = 654), II (N = 446) and IV (N = 764) were longitudinal cohort studies of patients having been treated as part of routine care during 2009-2014. Within-group effects and the influence of potential predictor variables on treatment response and adherence were estimated using multilevel modelling. In Study III (N = 126), non-inferiority of ICBT was evaluated against standard treatment (face-to-face cognitive behavioural group therapy; CBGT) four years after treatment using a randomised controlled trial (RCT) design, assessing changes in symptoms of SAD and yearly societal costs.

Results: In all studies, large (d = 0.8-1.3) improvements were observed after ICBT. Beneficial effects (i.e. reduced symptoms of social anxiety and co-morbid depressive symptoms and increased health-related quality of life) of treatment were maintained up to four years. When compared against standard treatment, ICBT was at least as long-term effective and cost-effective; although the estimated treatment cost of ICBT amounted to only 17% of the cost of CBGT, both interventions were equally effective and led to similar yearly societal cost reductions. Improvement slopes varied significantly between patients. High levels of treatment credibility and adherence were associated with better treatment response. Furthermore, higher illness severity predicted greater improvement but was also related to worse follow-up status.

Conclusion: ICBT can be successfully implemented in routine clinical care and is at least as effective and cost-effective as standard treatment for SAD, both short- and long-term. With its potential to significantly improve access to specialised mental healthcare, ICBT represents an important step forward in modernising healthcare systems through increased use of e-health.

SAMMANFATTNING

Bakgrund: Socialt ångestsyndrom är en vanligt förekommande psykisk störning som orsakar ett betydande lidande och som för många kan bli väldigt handikappande. Då det är vanligt förekommande leder det även till betydande samhällsekonomiska konsekvenser. En stor andel av drabbade individer går utan behandling, dels på grund av låg tillgänglighet till effektiv behandling men kan även bero på stigma och rädsla för att söka vård. Nyttan av kognitiv beteendeterapi (KBT) är väl etablerad, och nya innovationer inom e-hälsa såsom internetförmedlad KBT (IKBT) kan avsevärt öka tillgången till effektiv vård. Flera kontrollerade studier har visat att IKBT är både effektiv och kostnadseffektiv. Innan vidare spridning av IKBT inom den psykiatriska vården är det däremot viktigt att utvärdera dess kliniska effektivitet för att undersöka om behandlingsformatet fungerar som förväntat när det ges som reguljär behandling i en naturlig vårdmiljö.

Mål: Syftet med detta doktorandprojekt var att utvärdera den kliniska effektiviteten av IKBT vid behandling av socialt ångestsyndrom, att bedöma om den är minst lika verksam och kostnadseffektiv som standardbehandling samt att identifiera faktorer som kan förklara variationen i behandlingsresultat.

Metoder: Delstudie I (N = 654), II (N =446) och IV (N = 764) var longitudinella kohortstudier av patienter som behandlats som en del av reguljär vård under 2009-2014. Inomgruppseffekter och påverkan av potentiella utfallsprediktorer uppskattades med hjälp av flernivåanalys. I delstudie III (N = 126) utvärderades IKBT mot standardbehandling (KBT i grupp) fyra år efter avslutad behandling i form av en randomiserad kontrollerad studie. Förändringar i symptom på social ångest samt årliga samhällskostnader beräknades.

Resultat: I samtliga studier kunde stora (d = 0,8-1,3) förbättringar observeras efter genomgången IKBT. Uppnådda behandlingsresultat bibehölls i upp till fyra år, både när det gäller minskning av symtom på social ångest, depressiva symptom och hälsorelaterad livskvalitet. Vid jämförelse mot standardbehandling var IKBT var minst lika effektiv och kostnadseffektiv på lång sikt; trots att den uppskattade behandlingskostnaden för IKBT endast utgjorde 17% av kostnaden för standardbehandling var behandlingarna lika effektiva och ledde till liknande samhällsbesparingar. Det fanns tydliga skillnader i behandlingssvar mellan patienter. Hög grad av följsamhet samt hög upplevd trovärdighet av IKBT var associerat med bättre behandlingssvar. Dessutom var sjukdomens svårighetsgrad relaterad till behandlingssvar: högre sjukdomsgrad ledde till snabbare förbättring, dock var sjukdomsnivån också högre vid uppföljning.

Slutsats: IKBT kan framgångsrikt implementeras i reguljär klinisk vård och är minst lika effektiv och kostnadseffektiv som standardbehandling för behandling av socialt ångestsyndrom, både på kort och lång sikt. Då IKBT har en betydande potential att avsevärt förbättra tillgången till specialiserad psykiatrisk vård utgör behandlingen ett viktigt steg framåt för att modernisera hälso- och sjukvårdssystemen genom ökad användning av e-hälsa inom vården.

LIST OF SCIENTIFIC PAPERS

I. **El Alaoui S**, Hedman E, Kaldo V, Hesser H, Kraepelien M, Andersson E, Rück C, Andersson G, Ljótsson B, Lindefors N. Effectiveness of Internet-Based Cognitive-Behavior Therapy for Social Anxiety Disorder in Clinical Psychiatry. *Journal of Consulting and Clinical Psychology*. 83(5):902-914, October 2015.

II. **El Alaoui S**, Hedman E, Ljótsson B, Lindefors N. Long-term effectiveness and outcome predictors of therapist-guided internet- based cognitive-behavioural therapy for social anxiety disorder in routine psychiatric care. *BMJ Open*. 2015 Jun 23;5(6).

III. Hedman E, **El Alaoui S**, Lindefors N, Andersson E, Rück C, Ghaderi A, Kaldo V, Lekander M, Andersson G, Ljótsson B. Clinical effectiveness and cost-effectiveness of Internet- vs. group-based cognitive behavior therapy for social anxiety disorder: 4-year follow-up of a randomized trial. *Behaviour research and therapy*. 2014 Aug;59:20-9.

IV. **El Alaoui S**, Ljótsson B, Hedman E, Kaldo V, Andersson E, Rück C, Andersson G, Lindefors N. Predictors of Symptomatic Change and Adherence in Internet-Based Cognitive Behaviour Therapy for Social Anxiety Disorder in Routine Psychiatric Care. *PLoS One*. 2015 Apr 20;10(4).

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LIST OF ABBREVIATIONS

CBGT	Cognitive behavioural group therapy
CBT	Cognitive behaviour therapy
CI	Confidence interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
EQ-5D	EuroQoL-5 dimensions
ICBT	Internet-based cognitive behaviour therapy
ICER	Incremental cost-effectiveness ratio
LSAS	Liebowitz Social Anxiety Scale
MADRS	Montgomery Åsberg Depression Rating Scale
MINI	Mini International Neuropsychiatric Interview
QALY	Quality adjusted life years
RCT	Randomised controlled trial
SAD	Social anxiety disorder
SSRI	Selective serotonin reuptake inhibitor
TIC-P	Trimbos and Institute of Medical Technological Assessment Cost Questionnaire for Psychiatry
WTP	Willingess-to-pay

1 INTRODUCTION

1.1 MENTAL ILL-HEALTH IS A RISING CONCERN

Mental ill-health is one of the leading causes of disability worldwide (1), and approximately 40% of the population will at some point during their life need professional help for clinical anxiety or depression (2). Anxiety disorders are the most prevalent class of mental disorders (3), and among these, social anxiety disorder (SAD) is considered to be the most common (4, 5) with a 12-month prevalence in the range of 2.8%-7.1% and a lifetime prevalence of 5%-12.1% (6-8).[i] At the core of SAD is a fear of being scrutinized and negatively judged by others and act in a way that is embarrassing and humiliating. Affected individuals therefore tend to avoid feared social or performance situations, experience anxious anticipation of these or intense anxiety in them, to such a degree that problematic thoughts, behaviours and feelings interfere with their daily lives, occupational or academic functioning or with their social relationships (10).[ii] Many – about half of affected individuals in developed countries (6) – do not receive treatment. A central barrier to appropriate mental health care is low availability of trained personnel to deliver effective treatments (12, 13). As a result, there are significant personal (14) and societal (15) economic consequences.[iii] There have been attempts to estimate the costs of SAD. Such health economic evaluations are often performed from a societal perspective, meaning that in addition to healthcare costs, indirect costs such as sick-leave and productivity losses are also considered (15). In a study of individuals with SAD in the general population, it was estimated that the average annual societal cost was approximately €12 000 per person. This can be compared with an estimated annual cost of about €3 000 for non-affected individuals (15).

Considering the rising concern of mental ill-health, with yearly costs of over EUR 7 billion only in Sweden (17) due to lost productivity, healthcare consumption and social benefits, a major challenge for mental healthcare is to meet the growing need to treat and prevent mental illness in order to include as many as possible within the labour market.

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[i] Different rates reported between studies likely depend on different methodological approaches when diagnosing SAD (e.g. the specific threshold for disability) (4). Defining SAD depending on the degree of distress required has yielded similar variations in estimated prevalence rates, ranging between 1.9% and 15.6%, in a Swedish study (9).

[ii] When seeking treatment, patients are asked to describe their symptoms and how these affect their lives. Until recently, it was the patient who would determine whether their fears were rational, but as of DSM-5 it is now the clinician who determines whether the fears being described are proportionate in relation to the risk or consequences of negative evaluation (11). A further change in the updated diagnostic manual is the broadening of possible feared consequences as they now also include a fear of rejection or offending others in addition to the fear of being humiliated and embarrassed (11).

[iii] It has been estimated that the cumulative global economic loss due to mental disorders will amount to US$ 16.3 trillion between 2011 and 2030 (16). In Europe, the costs of mental disorders account for approximately 3.5% of GDP (17).

1.2 TREATMENT OF SOCIAL ANXIETY DISORDER

As for SAD, short-term symptom reduction can effectively be achieved with pharmacological therapy using Selective Serotonin Re-Uptake Inhibitors (SSRIs) (18).[iv] However, although a range of pharmacological treatments have been tested, many of these have reported negative side effects that may be considered unsafe or lead to physical dependence (19, 20). Instead, most individuals prefer psychological treatments (21). Cognitive behavioural therapy (CBT) – a problem focused and highly action oriented intervention – is not only considered as an alternative for those not responding to pharmacological therapy (18) but with its strong empirical support (22), CBT is gaining recognition as a first line treatment for SAD (23). CBT has a strong emphasis on modifying everyday behaviour and challenging the validity of maladaptive negative thoughts. Hence, CBT targets behaviours, emotions and cognitions – factors that are maintaining the disorder – through a collection of techniques such as psychoeducation, cognitive restructuring, exposure to feared situations and relapse prevention (22, 24). Effect sizes of CBT for SAD have been reported in the range of $d = 0.70$ (25) to $d = 0.86$ (26). A meta-analysis covering 21 trials found that the average treatment effect was $d = 0.83$ (27). When estimating the average effect of only those studies that used a control group, a meta-analysis of 16 trials yielded an average d of 0.74 (28). Thus, the effects tend to range between moderate to large, according to the commonly used threshold values proposed by Cohen [v]. CBT in group format (CBGT) seems to have the best empirical support with superior effects compared with for example treatment as usual (30), other psychological treatments (31), fluoxetine or pill placebo (32).

Despite the substantial evidence (33-35) of the effectiveness of CBT, there are several barriers to treatment, primarily the limited availability of trained therapists. There is also evidence that most people with SAD do not seek treatment (36). The very nature of SAD with its disorder-specific fear of social interaction may partially explain this avoidance (37). There may also be the issue of stigma associated with undergoing psychotherapy. Further, there are practical barriers such as difficulties accessing treatment due to remote locations for people living in

[iv] SSRIs are antidepressant medications that have both an anxiety reducing effect and that can also treat depressive symptoms. These effects are achieved by manipulating the activity of the brain chemicals serotonin and/or noradrenaline. SSRIs have several benefits when compared with benzodiazepines and are considered to be the first-line pharmacological treatment for SAD today due to its moderate effect sizes and favourable side-effect profile (18). Besides alleviating both anxiety and co-morbid depression, they do not cause dependence in the same way as benzodiazepines (although a withdrawal state can be experienced if discontinuation is not managed gradually) and can be used for long-term treatment. The disadvantages are mainly that patients may experience an initial *increase* in anxiety when starting treatment, and – as is generally the case with pharmacological treatment of mental disorders – there is a significant risk that symptoms of social anxiety will return when the medical intervention is discontinued.

[v] A statistical method of arriving at such a description is the calculation of Cohen's d which standardizes the difference between two means and compare it to 0. This difference is expressed in standard deviation units, which can be interpreted as small (0.2 of a standard deviation), moderate (0.5 of a standard deviation) or large (0.8 of a standard deviation) (29). As such, it provides a way of quantifying the effect of an intervention, comparable across studies using the same effect measure.

rural areas, long waiting lists, limited clinic opening hours, and also the cost associated with treatment.

Hence, there is a need for innovative solutions that may facilitate treatment seeking, increase access to effective treatment and also increase the *capacity* of healthcare providers to deliver treatment to more individuals (38, 39).

1.3 INTERNET-BASED COGNITIVE BEHAVIOURAL THERAPY

1.3.1 Improving healthcare delivery

With the emergence of e-health and internet interventions such as internet-based CBT (ICBT), most of the above mentioned barriers to effective care can potentially be overcome and the threshold for seeking help may be lowered (40). Since information technology is fundamentally altering not only the way societies work at large and how we communicate, its application within healthcare is also significantly changing and modernising the way patients interact with healthcare providers. Indeed, e-health is increasingly becoming recognised as the most promising approach to improve the quality of care, patient safety and the efficiency of healthcare delivery (41). As awareness of ICBT increases among healthcare providers, it is gaining interest as a new method of treatment delivery that could use limited therapist resources in a more efficient way and consequently increase access to effective psychological treatments within mental healthcare (42). The intervention itself is similar to standard treatment (i.e. face-to-face CBT) including methodology and core components such as education about social anxiety, safety-seeking behaviours, cognitive restructuring, behavioural experiments, exposure to feared situations, attention training and relapse prevention, with the major difference being the form of communication and the time used for therapist support (43). From a health economic perspective, an central benefit of ICBT, therefore, is its potential cost-effectiveness (44, 45) compared to conventional individual face-to-face psychotherapy, mainly because it requires less therapist time (42, 46, 47).

1.3.2 Efficacy and outcome predictors

Several independent research groups have studied ICBT for SAD to evaluate its efficacy in a number of controlled trials, and the results are promising (43, 48-56). Evidence suggest that ICBT is as efficacious as conventional face-to-face CBT, not only for SAD but for a wide range of mental disorders (34, 57, 58), and significant long-term effects of ICBT for SAD have been demonstrated for up to five years after treatment (59-61).

Attempts have also been made to identify patient characteristics that are associated with treatment outcome using predictive analytics. More knowledge of outcome predictors may help determine whether ICBT is likely to benefit all or only some individuals, and identify factors that may explain the significant variation in treatment response between patients. An important question is whether ICBT is suitable also for more severe cases, or whether they would benefit

more from high-intensity face-to-face therapy. Another question concerns the influence of co-morbidity (e.g. depressive symptoms) on treatment outcome. Although findings have not been consistent across studies, there are some interesting observations on the role of illness severity, co-morbid depressive symptoms and outcome [vi] that have been reported. For example, the level of symptom severity at baseline is typically related to the degree of severity at post-treatment (62, 63), although this association is less clear in regard to symptomatic change (64, 65). The role of co-morbid depressive symptoms has not been consistently determined across studies; evidence from both CBT (63, 66) and ICBT (67) have found co-morbid depressive symptoms to be related to worse outcome, whereas other reports of ICBT found no such relation (68). A recent study using a different analytical approach was able to provide an explanation of the seemingly contradictory results reported in the previous literature. By focusing on social avoidance and comorbid depressive symptoms, subgroups of patients having different degrees of a *combination* of these two risk factors were identified by using cluster analysis. It was found that just having a higher levels of co-morbid depressive symptoms was not a risk-factor of poor treatment outcome *in itself*, but rather its combination with also having a high level of social avoidance (69). Finally, there is also evidence that the perceived credibility of ICBT (67, 68) and the level of treatment adherence (52, 67, 68, 70-72) are positively associated with treatment outcome. Consequently, expecting the treatment to work may be a critical success factor, and there seems to be a clear dose-response relationship suggesting that the more of the treatment content that patients are exposed to the more they are likely to benefit.

1.3.3 Clinical effectiveness

Although the efficacy of ICBT for SAD has been demonstrated in numerous trials, clinical effectiveness studies within the context of regular care that aim to maximize external validity is an important element of clinical research (73). Accordingly, in order to see whether the results of RCTs can be generalized to patients within regular care, this doctoral project arose from the need to thoroughly evaluate the use of ICBT as a method of treatment delivery *in clinical day-to-day practice*. Since many patients do not achieve sufficient symptomatic improvement after ICBT (74), such an evaluation would also include the identification of variables associated with treatment response, as predicting the likely course of symptomatic change for different subgroups of patients might enable clinicians to provide more individualised care to meet different patient needs.

Knowledge of the clinical effectiveness of ICBT for SAD has been lacking and is important before dissemination within the public mental healthcare system. This thesis presents four studies that explore the clinical effectiveness of ICBT for SAD over the years that the treatment has been implemented as routine care at the Internet Psychiatry Clinic, Psychiatric Clinic Southwest at Karolinska University Hospital Huddinge, Sweden.

[vi] The operational definition of outcome may differ between studies, and may refer to either achieved *end state* (i.e. the level of symptoms after treatment) or observed *change* between pre- and post-treatment.

1.4 AIMS OF THE DOCTORAL PROJECT

The overall aim of this research was to evaluate whether ICBT can be successfully implemented in routine clinical care as an effective method of treatment delivery, and consequently whether it can be safely recommended for dissemination within the public healthcare system. Although this research has implications for the treatment of a broader range of psychiatric disorders, the focus of this investigation has been on evaluating the treatment of SAD. The specific aims of each study in this thesis are presented below.

1.4.1 Study I

The aim of Study I was to evaluate ICBT for SAD when implemented as routine care. That is, to validate its clinical effectiveness in a naturalistic setting. This evaluation would also include a comparison of the magnitude of treatment results over the years that the ICBT unit has operated.

1.4.2 Study II

The primary aim of study II was to evaluate the sustainability of treatment effects achieved after ICBT for SAD, and secondly to identify factors that influence long-term improvement.

1.4.3 Study III

The aim of Study III was to evaluate whether ICBT for SAD is at least as long-term effective and cost-effective as the standard treatment.

1.4.4 Study IV

The aim of Study IV was to identify factors that may explain differences in symptomatic improvement and treatment adherence.

2 METHODS

2.1 SETTING AND PARTICIPANTS

All of the studies were conducted at the Internet Psychiatry Clinic, Psychiatric Clinic Southwest at Karolinska University Hospital Huddinge, Stockholm, Sweden. Irrespective of whether patients were self-referred or referred by a general practitioner, they had to first register for treatment online through a public e-service portal for healthcare (i.e. Healthcare Guide 1177, formerly known as "Mina Vårdkontakter"). At the time of the studies, only patients that were residents in Stockholm County could register.[vii] A structured diagnostic interview with a clinician was required before treatment. Therefore, all patients who completed the online screening procedure were invited to the ICBT unit for a clinical visit. Besides meeting the DSM-IV criteria for SAD, a more general prerequisite for treatment inclusion was having a basic capability to assimilate the content of the treatment; since ICBT is highly dependent on patients' abilities to access, read and use web-based material on their own, having a minimum level of computer literacy and being able to read and write in Swedish was necessary.

Of those who completed the initial online screening for routine care (i.e. Studies I, II and IV), approximately 60% were included for treatment. There were several reasons reported by the medical staff for excluding patients after the initial clinical visit, the three most common being that the patient did not fulfil the diagnostic criteria for SAD or that SAD was not their *primary* diagnosis (around 30% of excluded patients), that patients themselves decided not to initiate the treatment (around 20%) or that the ICBT treatment format was considered to be suboptimal considering the level of clinical complexity (e.g. severe cases with high degree of comorbidity, around 15%). Less common reasons for exclusion, with occurrences in the range of around 2-4%, were for example substance misuse, moderate to high suicide risk, language difficulties or not attending the clinical visit. Sample sizes of patients included in Studies I-IV are summarized in Table 1 along with data on assessment completion.

Table 1. Study participants.

Study	Sample (N)	Provided follow-up data, N (% of included patients)		
		Post-treatment	6-month follow-up	Long-term follow-up
Study I	654	547 (84%)	172 (42%)	
Study II	446	391 (88%)	173 (39%)	321 (72%)
Study III	126	125 (99%)	119 (94%)	103 (82%)
Study IV	764	657 (86%)		

[vii] As of January 2015, a new patient law has made it possible also for patients residing outside of Stockholm County to register for treatment at the Internet Psychiatry Clinic.

In Studies I, II and IV, cohorts with available clinical data at the time of extraction were examined. Consequently, the differences in sample sizes between the studies shown in Table 1 reflects that somewhat different time periods were examined (e.g. Study IV was performed at a later point in time than Study I, when more patients had been treated at the clinic). Study II included only 446 patients since not all patients had fulfilled criteria for inclusion to follow-up data collection (i.e. they had to have completed treatment approximately one year earlier). These patients were thus invited to complete a follow-up assessment 1-4 years after treatment (M = 2.66 yrs., SD = 0.80). In Study III, out of 230 referred patients, 126 had met inclusion criteria and were included in the original RCT (53) and allocated to either ICBT (n = 64) or to GCBT (n = 62). The recruitment process is described in the original article (53). In the long-term follow-up study (i.e. Study III), these patients were contacted four years (M = 4.2 yrs., SD = 0.7) after treatment and were asked to complete self-report assessments online. Of the 126 participants included, 103 (82%) completed long-term follow-up assessments.

2.2 STUDY DESIGN

Although Study III was a follow-up of a previously conducted RCT, its purpose was to evaluate ICBT against standard treatment within a clinical setting. Studies I, II and IV were exclusively focused on examining how ICBT works after the treatment had been implemented as *routine* care.[viii] As such, these were characterised by a more naturalistic design, following large cohorts of patients over several years applying a methodological approach which concerned the exploration of patterns of symptomatic change over time. Also, since these were longitudinal cohort studies of registry-type data with no comparison group or randomization procedure involved, Study III therefore complemented Studies I, II and IV due to its controlled design.

2.3 OUTCOME MEASURES

The primary outcome measure was the self-report version of the Liebowitz Social Anxiety Scale (LSAS-SR) (75). Remission was operationalised as achieving a cut-off score of LSAS-SR ≤ 30, indicative of probable absence from social anxiety disorder (76). Secondary outcomes were co-morbid depressive symptoms and health-related quality of life. These were measured using the self-rated Montgomery-Åsberg Depression Rating Scale (MADRS-S) (77) and the EQ-5D (78). In addition, the level of treatment adherence, operationalised as the number of accessed treatment modules between pre- and post-treatment, was examined as an outcome predictor in Study I and as a dependent variable in Study IV.

[viii] Although the clinical setting was the same across all studies, the non-inferiority trial had somewhat stricter inclusion criteria. For example, not scoring > 20 on the MADRS-S was a criterion in the RCT (53), which can be compared with the significantly higher exclusion threshold of ≥ 35 on the MADRS-S when the treatment was offered as routine care. The mean pre-treatment level of depressive symptoms was 12.7 (SD = 6.5) in the RCT and 14.7 (SD = 7.5) in Study I.

2.4 ASSESSMENTS

Consistent with the operational routines at the ICBT unit, patients provided online self-assessments at the following occasions: at screening, at treatment start (pre-treatment), weekly during treatment, at the end of treatment (post-treatment) and finally at six months after treatment (6MFU). In addition, clinician-administered assessments were completed for all patients prior to treatment and patients were also invited to a follow-up visit after treatment. The screening procedure included the following set of online instruments: an initial assessment of the medical history adapted from The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), the LSAS-SR, the MADRS-S, the EQ-5D, the Alcohol Use Disorders Identification Test (AUDIT) (79, 80), the Drug Use Disorder Identification Test (DUDIT) (80-82), a questionnaire on healthcare consumption and productivity losses for patients with a psychiatric disorder (TIC-P) (83) and the World Health Organization Adult ADHD Self-Report Scale (ASRS) Screener (84). Additional information was collected by the medical doctor during the clinical visit including clinician-ratings of the LSAS and the MADRS. A structured diagnostic interview was also conducted using the Mini International Diagnostic Interview (MINI; 85).

2.5 STATISTICAL ANALYSES

A common analytic theme throughout the studies were the use of multilevel models, a relatively advanced type of regression analysis, to examine symptomatic change over time. To illustrate the relative complexity of the observations to be examined in Studies I, II and IV, Figure 1 shows the symptomatic patterns of change for a random selection of 100 patients. As can be seen, there are large variations in both initial symptom severity and in how the level of social anxiety changes over time.

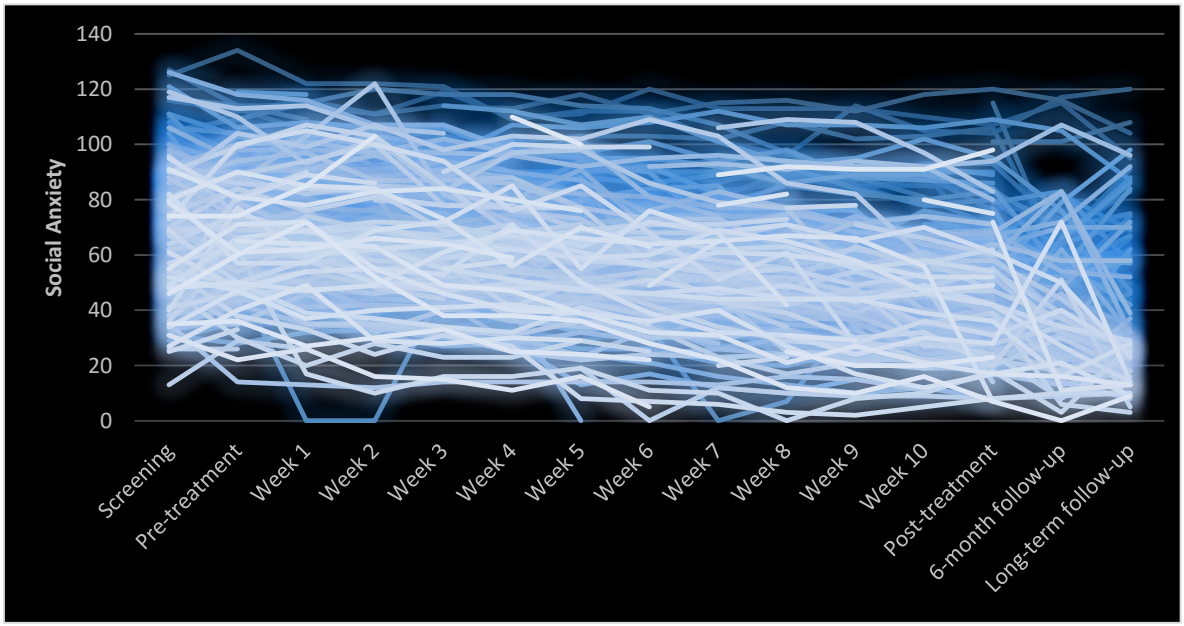

Figure 1. Observed symptomatic change over time for a random sample.

Multilevel modelling is particularly suitable for this type of longitudinal data with repeated measurements because the information is typically organised in more than one level (i.e. the data is hierarchical [ix]) and missing values is often an issue (86). Because observations are analysed on an intention-to-treat (ITT) basis, all patients are included in the analyses irrespective of how many measurements they have provided or whether they have dropped out before post-treatment assessment. As such, multilevel models use all available data, regardless of whether measurements are missing on some occasions. This is an advantage compared with traditional regression methods or analysis of variance (ANOVA), where cases that have missing data are typically deleted from the analysis (i.e. complete case analysis).[x] Another advantage is that the hierarchical structure of the data is accounted for in the computations of the estimates. This aggregated nature of the data is important to consider because it can affect the reliability of the results.

A multilevel approach was also applied when evaluating the influence of different variables on the regression slopes, that is, how they affect the rate of improvement. By using data collected during screening and during the clinical visit, a relatively large number of potential predictor variables could be explored. To systematically examine these predictors, we followed the procedure adopted by Fournier et al. (87) and Amir et al. (88) in which the variables were first screened for their prognostic value by analysing them in separate domains (socio-demographic variables, clinical characteristics, family history of mental illness and treatment-related factors) before including them into a final model containing only those variables who had a significant effect at the $p < .05$ level within each respective domain. Thus, in the final model, the effect of each predictor was estimated while controlling for the effects of the other predictors.

2.6 COST-EFFECTIVENESS

Since public health resources are limited, choices need to be made about how these should be allocated to provide the most benefit. Evaluating the relative cost-effectiveness of different interventions (e.g. between ICBT and standard treatment) is a way to guide such decisions, as a cost-effectiveness analysis (CEA) can estimate the likely benefits and costs of an intervention relative to the alternative (89). In Study III, one objective was to estimate the long-term cost-effectiveness of ICBT. Given the significant amount of indirect costs associated with SAD (90), a societal perspective was adopted to evaluate societal economic gains achieved through ICBT (15). The main outcome of the CEA was the incremental cost-effectiveness ratio (ICER) which is the ratio of the costs to the health effects between ICBT and CBGT (89). The ICER, therefore, is an estimation of the additional cost for each treatment responder or for each quality

[ix] Since each patient provides several measurements over time, these data are organized at several levels. For example, each set of repeated LSAS-SR scores (Level 1) are related to a specific patient (Level 2).
[x] Imputation of missing values is also an option in these cases.

adjusted life year (QALY) gained. Visually, the ICER can be illustrated using the cost-effectiveness plane (91). This plane (Figure 2) can be divided into four quadrants, each having a different implication for the economic evaluation of the intervention and consequently for decision makers. ICERs located in the south-east quadrant implies that the intervention is more effective while less costly than the alternative, thereby always considered as cost-effective. At the opposite end, in the north-east quadrant, the costs and effects are all worse than the alternative (i.e. more costly and less effective). In such a scenario, the intervention can never be considered as cost-effective. Finally, in the north-east and south-west quadrants, the cost-effectiveness depends on the willingness to pay (WTP) [xi] for each responder or for each QALY gained. In Figure 2, the slope of the line between the standard treatment (at the centre of the diagram) and the ICBT point estimate indicates the cost-effectiveness ratio. Since the cost-effectiveness ratio is the slope that extends from the origin (which is the treatment option that ICBT is being compared with) to an estimated cost-effect combination of the ICBT option, we can see that the cost-effectiveness of ICBT is always evaluated against an alternative. Thus, in a CEA, a treatment can never be cost-effective in itself, only in relation to another treatment option and to the willingness to pay (illustrated as the dashed line in Figure 2).

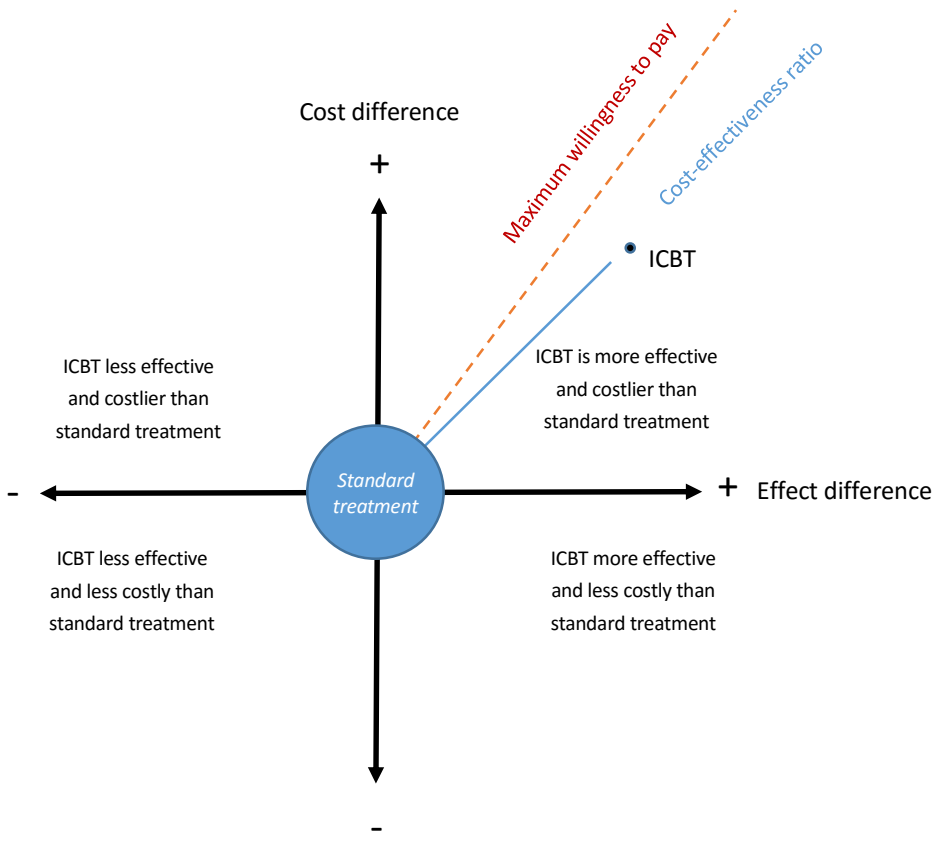

Figure 2. The cost-effectiveness plane. Adapted from Black (1990).

[xi] As guidelines for what might be regarded as good value for money, there are frequently used thresholds of the WTP for health effects, also known as the maximum acceptable ceiling ratio (92). These tend to vary between countries. For example, the National Institute for Health and Clinical Excellence (NICE) in the UK values the cost per QALY at £20 000-£30 000 (€22 000-€34 000; $30 000-$45 000) and in the USA, this threshold is typically $50 000 per QALY. If a treatment costs less that the threshold value, the treatment is typically considered cost-effective.

There will always be some degree of uncertainty around the estimated ICERs (93). In Study III, this uncertainty was reported both as a confidence interval (CI) around the estimate and also graphically as a cost-effectiveness acceptability curve (CEAC). Also, a cost-effectiveness plane was presented as a scatter plot [xii] of a large number of mean differences in costs and effects to provide an illustration of the uncertainty surrounding the estimated difference in cost and effect of ICBT compared to the alternative.

2.7 ETHICAL CONSIDERATIONS

All studies were approved by the Regional Ethical Review Board in Stockholm, Sweden. The risks of this research has been considered to be relatively small compared to the potential benefits. Written informed consent was obtained from all participants in Study III. Studies I, II and IV were retrospective cohort studies; participants were thus informed about the research and given the choice of participation through an opt-out methodology. This is generally considered to be the most efficient procedure for using registry data, an approach that increases the likelihood of having a more representative sample (94) while not violating the option of providing choice (95). For increased protection of privacy during internet communications, data traffic was secured using 128-bit Secure Sockets Layer (SSL) encryption, which corresponds to the same level of protection commonly used by banks for financial transactions. Further, patients logged into the treatment system via the public healthcare portal (Mina Vårdkontakter), which applied a log-in procedure in accordance with The National Board of Health and Welfare (Socialstyrelsen) and The Swedish Data Protection Authority (Datainspektionen) regulations.

[xii] 5000 ICERs were generated using nonparametric bootstrapping.

3 RESULTS

This chapter presents the results of the Studies. The following chapter will then discuss these findings within the context of the literature and their implications.

3.1 SUBJECTS

The mean age was around 33 years and the gender distribution was approximately 55% females. About half of the subjects were married or living in a relationship. The educational level was relatively high, with about 60% of patients having university level studies. Most patients (approximately 90%) were self-referred. About 50% were working full-time, 8% were unemployed and students constituted a significant proportion (22%).

3.2 STUDY I

Effectiveness of Internet-Based Cognitive-Behaviour Therapy for Social Anxiety Disorder in Clinical Psychiatry

Large reductions in social anxiety after treatment (effect size d = 0.86) with sustained improvements at 6-month follow-up (d = 1.15) were observed (Figure 3). Although only 20% of patients had achieved remission (LSAS-SR ≤ 30) immediately after treatment, this figure had increased to 36% at 6-month follow-up, suggesting that patients continued to improve after the therapist-guided treatment phase of 12 weeks.

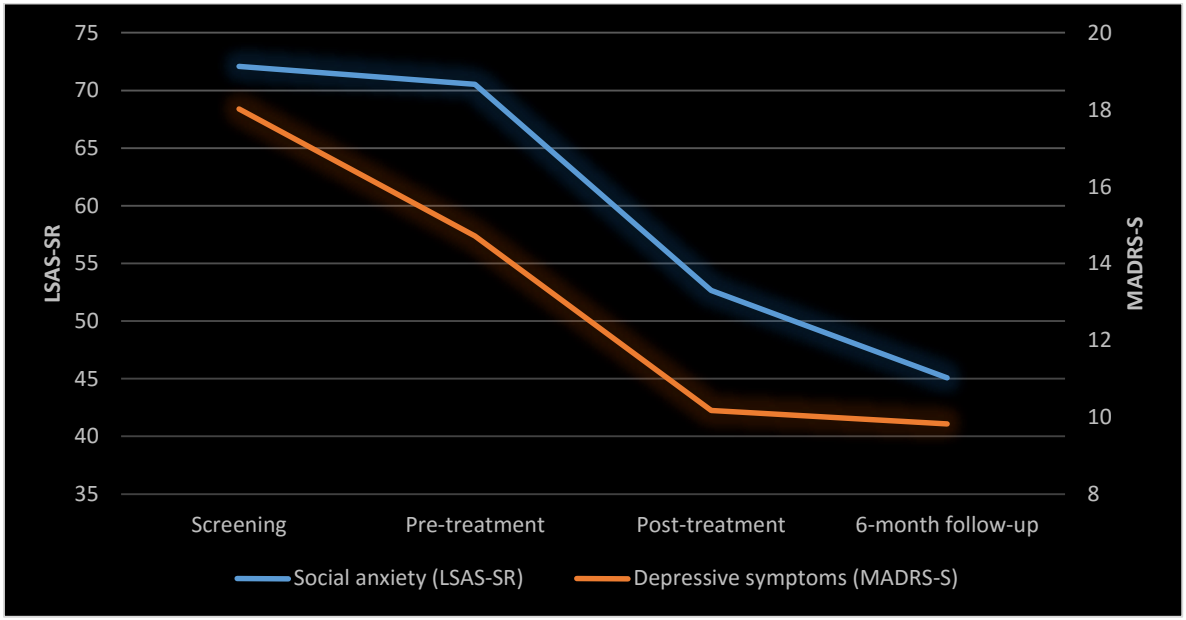

Figure 3. Estimated change in social anxiety and co-morbid depressive symptoms. Abbreviations: LSAS-SR, Liebowitz Social Anxiety Scale-Self-report; MADRS–S, Montgomery-Åsberg Depression Rating Scale–Self-Report.

A yearly increase in the rate of improvement was also observed (see *Figure 3* in the published article); three years after treatment implementation, the average LSAS-SR post-treatment score was about 16 points below the estimated end point score during the first year. In addition, the level of treatment adherence was related to the rate of improvement (i.e. the more modules patients completed, the more they benefited from the treatment).

Co-morbid depressive symptoms were significantly improved after treatment, with a moderate pre-post effect size of d = 0.56 (Figure 3). Noteworthy is the significant spontaneous improvement observed between screening and start of treatment (a waiting-time of approximately 2-3 weeks), corresponding to a moderate effect size of d = 0.57, which was similar to the degree of improvement achieved during treatment. Finally, the average level of satisfaction with the treatment was about 80%.

3.3 STUDY II

Long-term Effectiveness and Outcome Predictors of Therapist-guided Internet-based Cognitive-behavioural Therapy for Social Anxiety Disorder in Routine Psychiatric Care

Long-term improvements in both social anxiety (d = 1.17) and co-morbid depressive symptoms (d = 0.67) were observed up to four years after treatment (Figure 4). Although most of these improvements were achieved during treatment, patients continued to improve for up to four years after treatment.

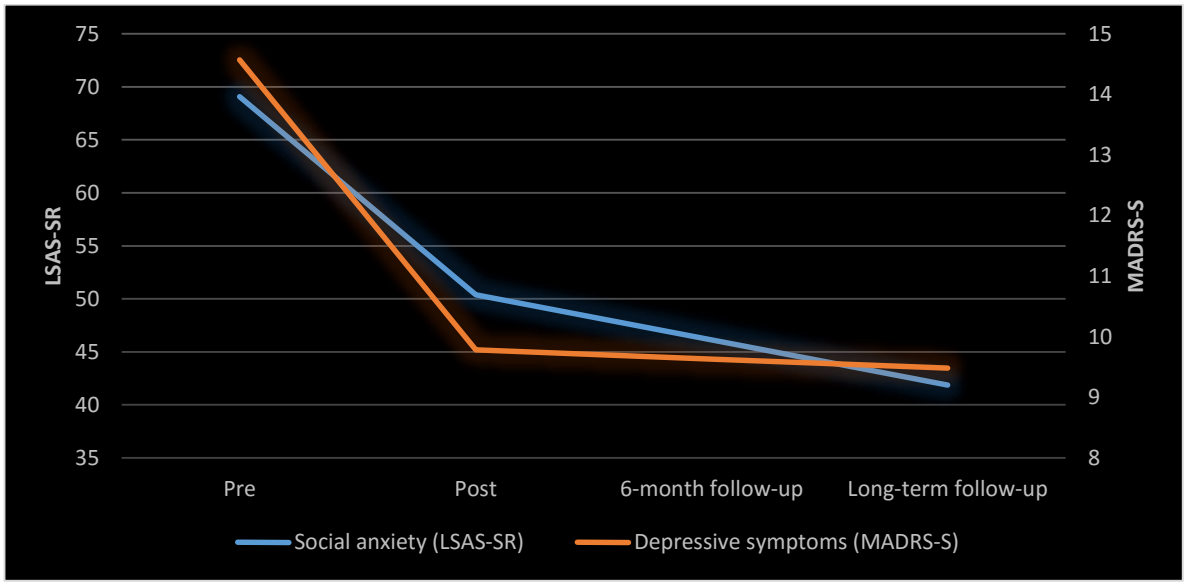

Figure 4. Long-term course of improvement in social anxiety and depressive symptoms after internet-based cognitive behavioural therapy in routine care. Abbreviations: LSAS-SR, Liebowitz Social Anxiety Scale-Self-report; MADRS–S, Montgomery-Åsberg Depression Rating Scale–Self-Report.

Patients also improved in health-related quality of life (*d* = -0.25) (Figure 5).

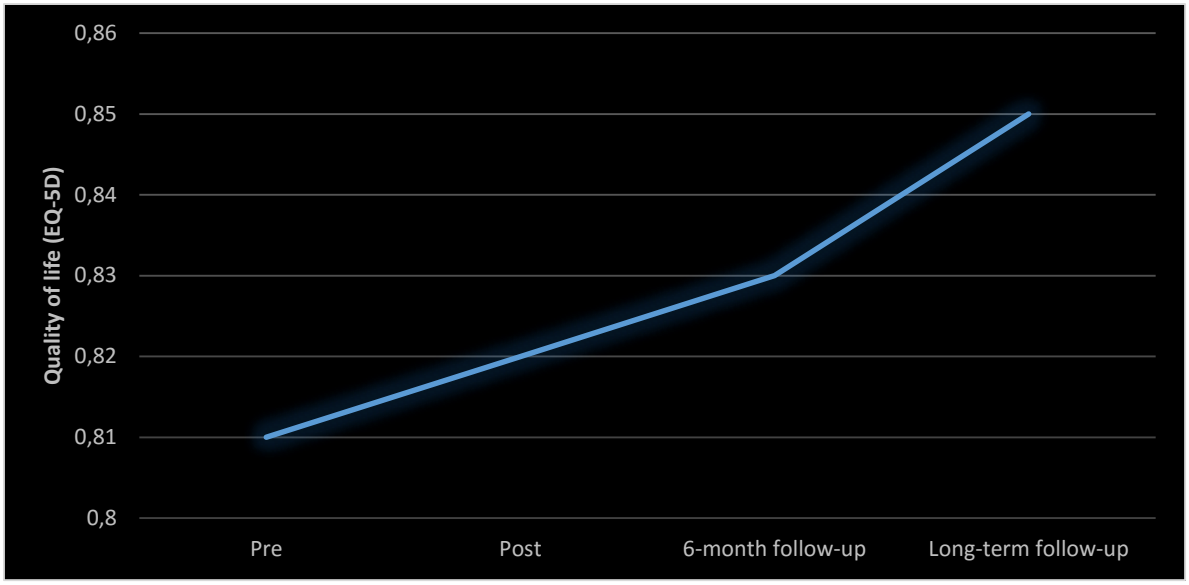

Figure 5. Long-term course of improvement in quality of life after internet-based cognitive behavioural therapy in routine care. Abbreviations: EQ-5D, EuoroQol five dimensions.

Finally, the rate of long-term symptomatic change varied significantly between individuals. A faster rate of improvement was observed among patients having a higher illness severity at baseline. Further, a slower rate of improvement was observed among those who reported having a family history of social anxiety.

3.4 STUDY III

Clinical Effectiveness and Cost-effectiveness of Internet- vs. Group-based Cognitive Behaviour Therapy for Social Anxiety Disorder: 4-Year Follow-up of a Randomized Trial

Large improvements (*d* = 1.34–1.48) were observed at 4-year follow-up on the primary outcome measure (LSAS-SR) in both ICBT and standard treatment (CBGT), differing only within the equivalence margin.

The CEA indicated that both treatments were equally cost-effective four years after treatment, which is reflected in the estimated probability of 62% that ICBT is a cost-effective treatment long term relative to CBGT at a WTP $0 for one additional QALY, marginally increasing to 64% at a WTP of $100 000. Specifically, both treatments were equally effective in terms of health improvements and similar reductions in indirect costs were observed. Societal gains were primarily caused by lower costs of unemployment. Total costs in both conditions were reduced by approximately half compared to pre-treatment (Figure 6).

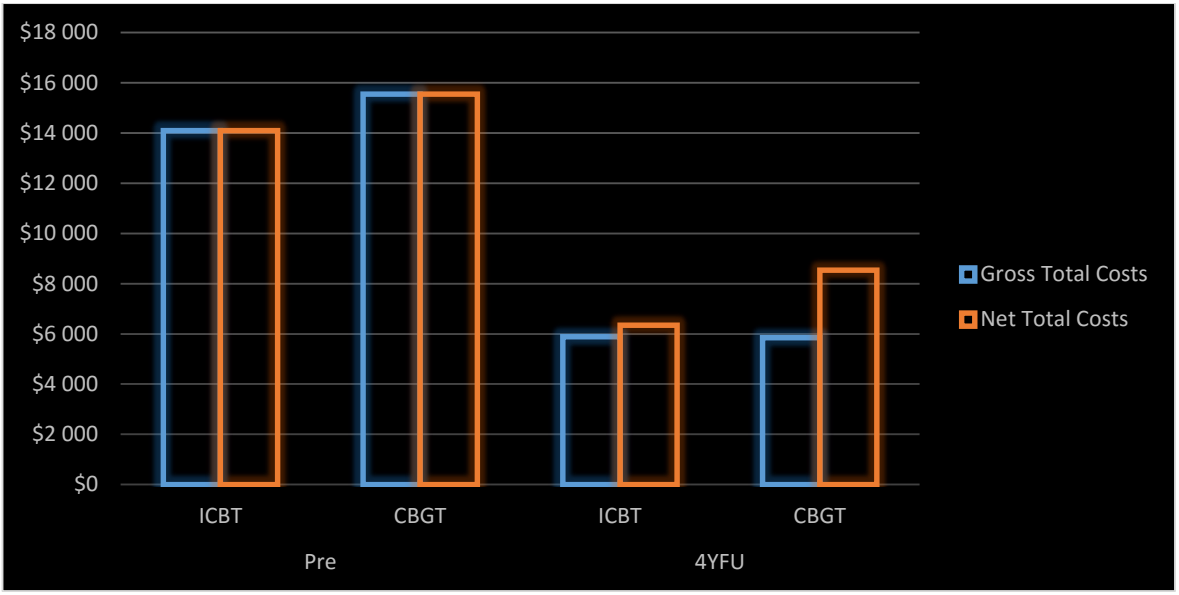

Figure 6. Total Cost of ICBT and standard treatment (CBGT). Net total costs include interventions costs. Abbreviations: ICBT, Internet-based cognitive behaviour therapy; CBGT, Cognitive behavioural group therapy; Pre, before treatment; 4YFU, four years after treatment.

3.5 STUDY IV

Predictors of Symptomatic Change and Adherence in Internet-Based Cognitive Behaviour Therapy for Social Anxiety Disorder in Routine Psychiatric Care

Results from Study IV indicate that the two most important factors that were associated with a faster rate of improvement (i.e. a steeper slope of the linear regression line) during treatment were treatment credibility (patients' beliefs and expectations about the treatment) and the level of adherence (number of accessed modules). In addition, a slower rate of improvement (i.e. a flatter slope) was observed among patients having a higher overall functioning level at baseline. The amount of therapist time spent was also negatively associated with outcome.

Having a family history of social anxiety was associated with greater treatment adherence, whereas having ADHD-like symptoms, being male, and having a family history of minor depression were related to a somewhat lower level of adherence.

4 CONCLUSIONS AND IMPLICATIONS

The overall aim of this research was to evaluate ICBT for SAD when implemented in routine outpatient care. The specific aims of each study was to:

- Validate the clinical effectiveness of ICBT for SAD in a naturalistic setting.
- Assess the long-term effectiveness of ICBT for SAD and identify long-term outcome predictors.
- Evaluate whether ICBT for SAD is at least as long-term effective and cost-effective as standard treatment.
- Identify factors that are related to sympomatic change and treatment adherence.

We will now turn to a discussion of the implications of the findings and discuss some limitations of the studies. Finally, some avenues for further research are suggested.

4.1 CONCLUSIONS ABOUT EACH RESEARCH QUESTION

4.1.1 ICBT can be successfully implemented in routine clinical care

As was indicated in the introduction, there has been a knowledge gap in regard to the clinical effectiveness of ICBT for SAD. Results from Study I suggest that ICBT for SAD is clinically effective and can be successfully implemented in routine outpatient psychiatric care. Further, the collective evidence from the studies in this thesis, coupled with two recent effectiveness studies conducted in Australia (96, 97) – also having relatively large patient samples –provide a good basis on which to establish the clinical effectiveness of ICBT for SAD by independent research groups. The recently published Australian study included 560 patients, in which ICBT was evaluated both when patients were guided by their primary care practitioner in the community or by a specialist clinician as in Studies I-IV. There were similar effect sizes in both types of supervision (d = 0.99 – 1.09) which are in the same range as the observed effects in Study I (d = 0.86 – 1.15). These are all large treatment effects, comparable to standard CBT with an average treatment effect of d = 0.83 (27). The patient satisfaction rate of 80% observed in Study I also indicate that ICBT is highly acceptable among those who provided post-treatment feedback.

An interesting observation in Study I was the yearly increases in treatment effects. Since these could not be explained by baseline clinical and demographic patient characteristics that were tested as co-variates, these yearly improvements might be attributed to the accumulation of clinical experience in delivering ICBT.

A final comment on the symptomatic changes observed in Study I was the timing of the improvements in co-morbid depressive symptoms. As can be seen in Figure 3, there was a slight left shift relative to improvements in SAD symptoms, suggesting that depressive mood is perhaps affected faster than changes in socially avoidant behaviour. The reverse is usually

observed in the treatment of depression, where mood tends to improve at a slower rate than the psychomotor retardation (98).

4.1.2 Beneficial effects are maintained

Both Studies II and III demonstrated that treatment effects achieved after ICBT may be sustained for up to four years, not only in regard to symptoms of SAD but also co-morbid depressive symptoms and health-related quality of life. The long-term effect size of d = 1.2 observed in Study II is very similar to that observed in previous follow-up trials with effects of d = 1.3 at 2.5 years post-treatment (60) and d = 1.3 after 5 years (59) after treatment. To my knowledge, Study II was the first long-term follow-up study of ICBT for SAD when provided as routine psychiatric care. As such, it provides evidence of the sustainability of ICBT for SAD in clinical practice.

4.1.3 ICBT is as long-term effective and cost-effective as standard treatment

In Study III, long-term effects of ICBT were evaluated against standard treatment. Results showed that ICBT had a large treatment effect and that the differences between the two interventions were within the non-inferiority margin. The results are in line with previous empirical findings investigating the long-term effects of ICBT for SAD, where outcome was measured at 30 months (60) and 5 years (59) after treatment, with effect sizes of d = 1.30 and 1.34, respectively. I therefore conclude that ICBT is at least as long-term effective as standard treatment for SAD. In addition, patients in both treatments achieved moderate improvements in co-morbid depressive symptoms.

In a recent systematic review of economic evaluations of internet interventions (99), it was concluded that for most conditions, internet interventions seem to have a "favourable probability" of being more cost-effective than control conditions. In Study III, however, this favourable probability appeared to decrease in proportion to the timeframe being considered; although the *intervention* costs for ICBT amounted to only 17% of the costs of standard treatment ($464/patient vs $2 687/patient), both treatments resulted in similar long-term reductions in overall societal costs. In both interventions, lowered costs related to unemployment were the main drivers of these societal gains. As such, treatment of SAD mainly seems to affect indirect costs. Indeed, at baseline, the proportion of indirect costs was as high as 86% of total costs.[xiii] This may be compared with the observations in a recent study where indirect costs of SAD amounted to 77% of total costs (90). Thus, it appears that the costs associated with SAD are first and foremost caused by lower productivity and work loss rather

[xiii] Baseline total costs for participants in the ICBT condition was estimated at $14 096. Of these, $12 118 were indirect costs (unemployment, sick leave, work cutback and domestic). The ratio of indirect costs to total costs can therefore be calculated as $12 118 / $14 096 = 86%.

than healthcare utilization, an observation that also seems to be congruent with the relatively low treatment seeking behaviour observed within this group.

A second conclusion from Study III, therefore, is that ICBT is at least as long-term cost-effective as standard treatment as both interventions lead to large improvements in social anxiety while reducing societal costs. Considering that ICBT enables each therapist to have up to 4 times as many patients in treatment simultaneously compared to standard treatment, I also conclude that ICBT is a good option for increasing treatment accessibility.

4.1.4 ICBT may be suitable also for those with more severe social anxiety

As was discussed in Chapter 1, the evidence regarding illness severity and its relation to treatment outcome has been relatively inconclusive. For example, a review (64) on outcome predictors for conventional CBT in the treatment of SAD reported that higher baseline severity predicted a higher end state of social anxiety (which was also observed in Study II), but concluded that illness severity was not associated with the degree of improvement. Results from Study II (Figure 7) suggest that the greater symptom severity before treatment, the higher the end state *but also* the steeper the improvement trajectory. A similar pattern has also been observed elsewhere where 2049 patients were treated with ICBT for anxiety and depression (100). Thus – and perhaps contrary to common beliefs regarding internet-delivered therapies – ICBT seems to work well in terms of symptomatic improvement also for patients who are more severely ill, although these patients may be less likely to achieve actual *remission* from SAD (which has also recently been observed elsewhere (69)). It might even be the case that the internet-based format of ICBT is particularly suitable for patients with social anxiety who might otherwise refrain from seeking care. However, we need to exercise caution when making treatment recommendations based on illness severity, considering recent findings showing that having a combination of high social avoidance (which constitutes one of the two LSAS subscales measuring illness severity) and high co-morbid depressive symptoms significantly increases the risk for poor treatment response (69).

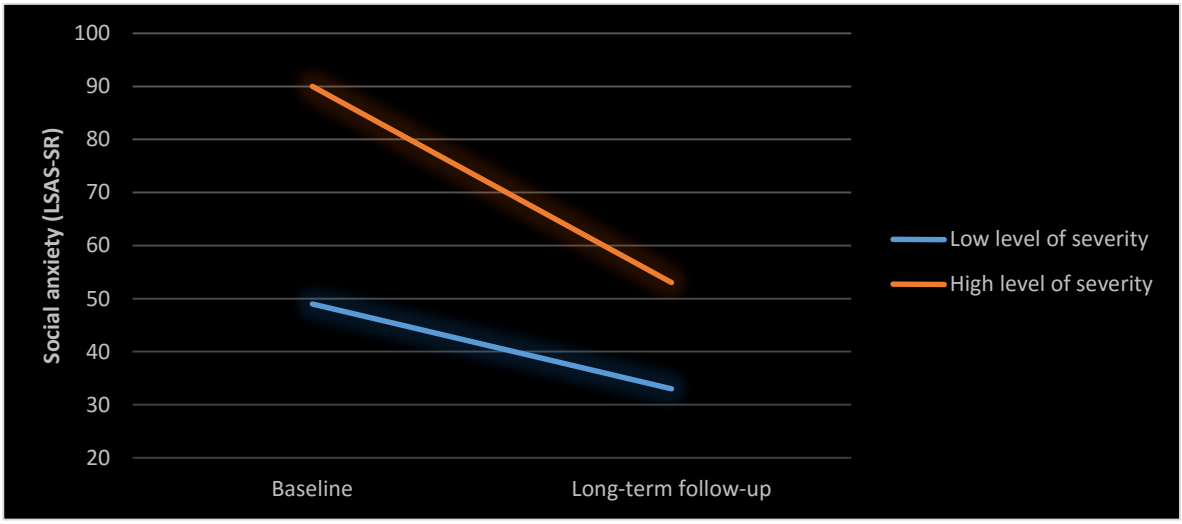

Figure 7. Predicted long-term improvement based on illness severity. Abbreviation: LSAS-SR, Liebowitz Social Anxiety Scale-Self-report.

4.1.5 Adherence predicts improvement

As has been established above, ICBT is clinically effective in the treatment of SAD. Based on the additional findings of Study IV, it can also be concluded that to benefit from ICBT, patients are recommended to comply with the treatment as prescribed. There are additional accounts in the literature where a similar association between adherence – either to face-to-face CBT or to ICBT – and treatment outcome has been observed (52, 67, 68, 70, 71). To complement the illustration of the effect of adherence on improvement as depicted in Fig. 2 in the published article of Study IV, I have also made a sub-group analysis using the data set from Study II (N = 654) in which patients have been categorized by those who completed all modules and those who did not, respectively. A significant difference in improvement rates could be observed (Figure 8) where completers (n = 243) evidenced a large pre-post effect size of *d* = 0.99, 95% CI (0.86,1.12) whereas non-completers (n = 301) achieved only about half of that effect; *d* = 0.55, 95% CI (0.46, 0.65).

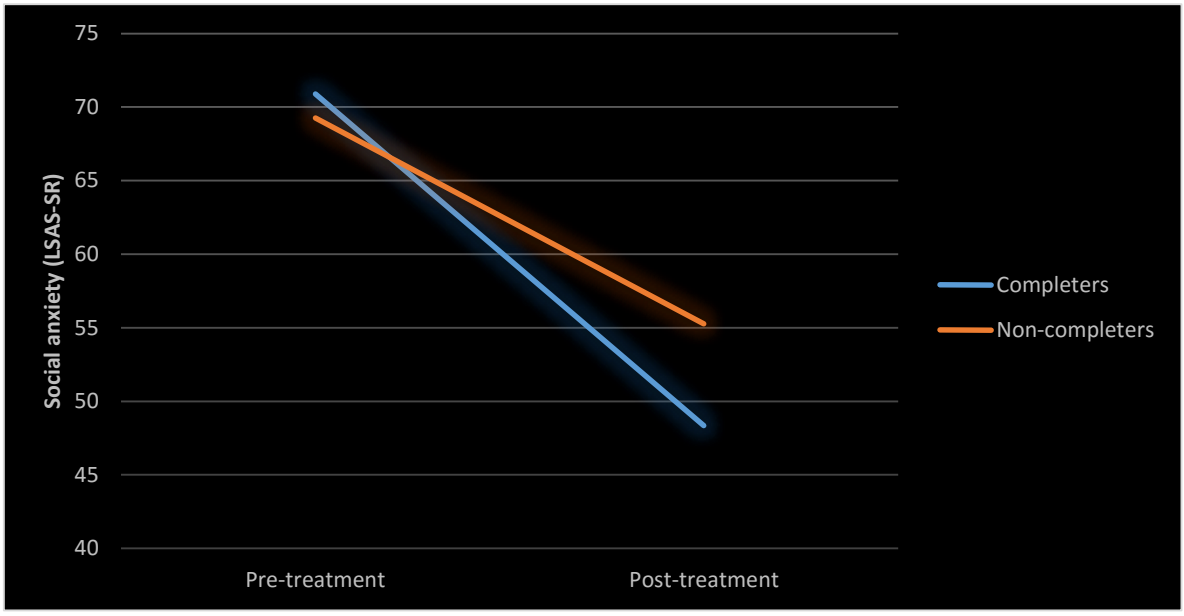

Figure 8. Change trajectories of completers vs non-completers. Abbreviation: LSAS-SR, Liebowitz Social Anxiety Scale-Self-report.

Since large variations in the level of adherence between patients were observed, and consequently variations in how much they benefit from the treatment, future research may focus on investigating strategies that may maximise adherence. This may be especially important in unguided version of ICBT where the level of adherence is often lower than when guided by a clinician (42, 101).

4.1.6 Treatment credibility is related to improvement and adherence

Evidence from Study IV and from previous observations (67, 68) suggests that the perceived credibility of the intervention is important for achieving a positive result. Since it was also found that credibility was strongly associated with the level of adherence, it may be the case that expecting that the treatment will be helpful is an important prerequisite for engaging in the treatment, consequently increasing exposure to effective CBT components. Interestingly, it has been observed elsewhere that having a pre-treatment interview in itself seems to improve treatment adherence (102). It is therefore possible that the diagnostic interviews that were conducted at the Internet Psychiatric Clinic prior to treatment could have had an influence on the perceived credibility of ICBT, consequently having had a positive effect on motivating patients to engage in the treatment. Confronting feared situations is difficult for anyone, but confidence in a method might have helped patients to feel more comfortable in going against many of the thoughts and feelings that were maintaining the disorder. It is also possible that the level of treatment credibility might have been related to the degree of early response as credibility was not measured until the second week of treatment. As a result, it is difficult to say for certain how patients would have rated treatment credibility prior to or during the initial diagnostic clinical meeting (hence being more useful as a prognostic indicator). The relation between early response and outcome of ICBT has been examined in a recent study (103) although symptomatic measurement at week *four* was then found to be the optimal occasion to predict outcome.

4.2 IMPLICATIONS FOR PUBLIC SECTOR POLICY AND PRACTICE

The collective evidence presented within this thesis may have a number of implications for public mental healthcare and practice. These will be discussed below, and mainly concern the following areas:

- National dissemination of ICBT
- Allocation of therapist resources
- Assuring and improving the quality of care

4.2.1 National dissemination of ICBT

As Swedish policy makers recognise the need for management and prevention of mental illness and the implications for the labour market, national dissemination of effective and resource-efficient treatments such as ICBT is hopefully becoming recognised as a viable option with potential to meet the growing need for treating mental disorders. E-health is now a central part of the healthcare strategy among Swedish municipalities, county councils and regions as a means to increase quality, to achieve a more equitable care and to use healthcare resources more efficiently. A promising initiative that has been undertaken is the current development of a national IT platform (*Internetbaserat stöd och behandling*) for internet-based support and treatment, intended for use by healthcare staff and patients within the public healthcare. Several

county councils have already expressed interest in participating in a collaborative effort to offer ICBT for its community members. As a first step, a plan for dissemination and development of ICBT may therefore include a nation-wide implementation of those treatments that, to date, have been clinically evaluated in routine care, e.g. the treatment for SAD evaluated in Studies I-IV and treatments for depression and panic disorder (104, 105). Ideally, ICBT providers should aim to report key outcome measures to a national quality registry for internet interventions as this would allow for easy identification of best practice through outcome comparisons between clinics, thereby stimulating learning and continuous quality improvements. Such a register (*Svenska internetbehandlingsregistret, SibeR*) is currently under development with a pilot implementation initiated during 2015.

4.2.2 Allocation of therapist resources

A second aspect concerns the optimal use of trained therapists as they are in limited supply. I believe that the two following circumstances render it likely that therapists will have a more *supervisory* role in the future rather than that of directly treating patients:

1. We are in the middle of an e-learning paradigm shift in which teaching and learning is increasingly conducted online (106).
2. A growing body of research indicate that self-guided internet-based treatments (optimally coupled with intelligently designed automated feedback) may yield results comparable to therapist-guided treatments (43, 44, 48-53, 55, 56, 59, 60, 107-111).

Hence, the trend of e-health and internet-based interventions within mental healthcare points towards an increasing standardisation and *automation*, as such increasing the distance between patients and therapists similar to that of students and teachers within the educational system through online distance learning. This is a logical consequence of having limited human resources (therapists/teachers) while providing services (treatments/courses) to an increasing number of individuals in need of these services. From a utilitarian perspective, this development might be considered as good since it strives to maximise the utility and well-being of the population by allowing more people to access effective care. Still, the role of the therapist is an ongoing debate, where some argue that therapist support is necessary for achieving acceptable treatment gains (112) based on evidence of poor response when guidance is not provided (58). We also observed in Study IV that therapist time was negatively associated with the speed of recovery. This may suggest that patients who have difficulties are also in need of more specialised therapist support throughout treatment and that less active patients may require therapists to invest more time to motivate patients. Then again, there is evidence that finds no support for the assumption that guidance from a therapist is necessary for improvement; for example, an interesting finding was that adding live exposure sessions to an ICBT treatment did nothing to improve the outcome (54). On the whole, it seems that, at least for *some* patients, therapist guidance in ICBT may not be as necessary for achieving a treatment response as we might have assumed. Indeed, in a recent review covering 37 RCTs, it was concluded that guidance may not be required to achieve immediate gains through ICBT,

although guidance and support may help maximize treatment adherence (113). It was also noted that the clinical experience of the person providing support does not seem to have any effect on treatment success.

Since therapist support may be needed for some but not all patients, if follows that limited therapist resources should optimally be allocated where it is needed the most, possibly through some selection criteria. An example of this line of reasoning is the application of a stepped care approach (39). In Figure 9, I provide an example of how treatment delivery could be configured based on the amount of support needed. The benefits, costs and potential drawbacks of such an approach should, of course, have to be evaluated. In addition, criteria for allocating patients between steps have to be determined.

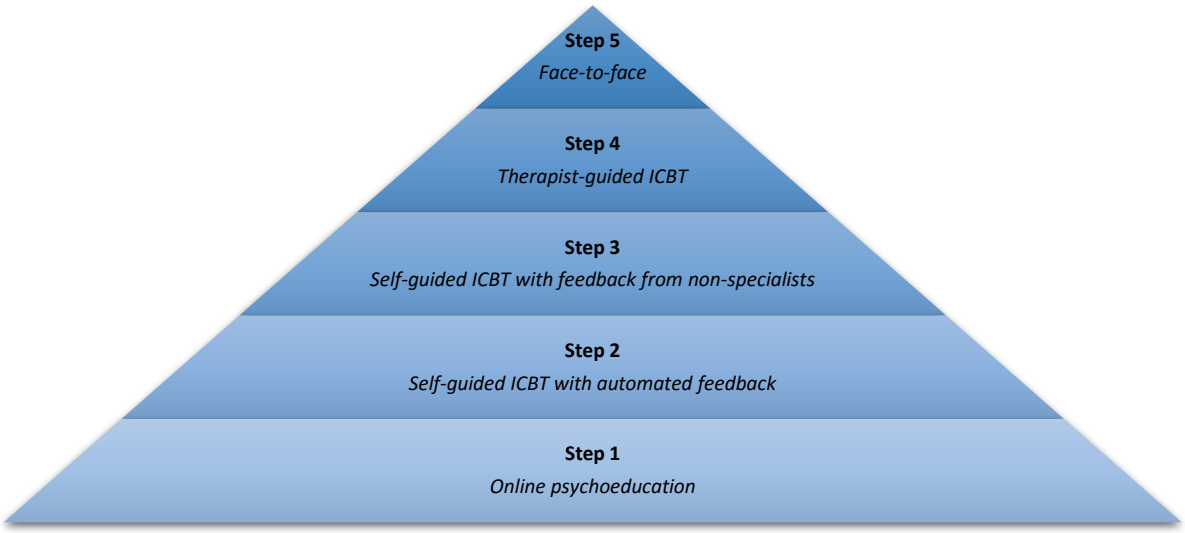

Figure 9. A stepped-care approach to internet-based treatments.

I am aware of two studies in which a stepped care approach to ICBT for SAD has been previously investigated. In the first study, Berger and colleagues (48) compared three types of support within a randomised controlled trial. In one of the treatment arms, the level of therapist support was flexible and stepped up as demanded by the patients. Interestingly, there were no significant differences between treatment conditions, neither in terms of improvements in symptoms of SAD nor in treatment adherence; patients in all treatment arms achieved large improvements with a mean effect size of d = 1.47. In the second study, recently published by Haug and colleagues (114), a stepped care approach including psychoeducation, ICBT and face-to-face CBT was evaluated against standard face-to-face CBT. A purpose of the study was to identify moderators of treatment outcome between face-to-face CBT and stepped care, i.e. to see if baseline characteristics might indicate whether one treatment approach is more beneficial than the other for different subgroups of patients. However, no selection criteria for recommending one form of treatment over the other could be defined. Hence, further research is needed in order to determine patient factors that may indicate whether high-intensity CBT

(e.g. face-to-face CBT) would be more helpful than low-intensity CBT (e.g. unguided or guided ICBT).

4.2.3 Assuring and improving the quality of care

Within the mental healthcare system, systematic and structured monitoring of processes and patient outcomes is needed to assure the quality of care and patient safety. However, current electronic medical records and systems are mostly used for administrative purposes. Since ICBT was first implemented in regular care, the ICBT unit at Psychiatry Southwest has systematically registered the course of illness and treatment outcomes for all treated individuals which allows for performance monitoring and continuous assessment of the quality of care. The ICBT unit could therefore be considered as an example of a process-based quality management system for mental healthcare that can provide a basis for a discussion about best practices between caregivers regarding the provision of e-health interventions to treat psychiatric disorders. The quality register for internet interventions, SibeR, may further provide future transparency in treatment outcomes and quality indicators between healthcare providers. Increased awareness of best practices and also differences in clinical practices and outcomes may therefore be achieved. Ideally, this would in turn lead to organisational learning and continuous improvements in the quality of care and in patient outcomes.

4.3 LIMITATIONS

In this section, I will discuss a selected number of potential limitations.

4.3.1 Controlling for spontaneous recovery

None of the four studies had a waiting list control group, which makes it difficult to control for possible spontaneous improvement and the effect of time. Although a waiting list would have been ideal to assure that the observed improvements may be attributed to ICBT, such limitations were more or less unavoidable in Studies I, II and IV considering that these were retrospective cohort studies aimed at evaluating how ICBT works in a naturalistic setting. Also, empirical evidence renders it unlikely that the observed effects can be explained by spontaneous recovery, for example:

- SAD is considered to be a chronic condition if untreated (115);
- meta-analytic evidence suggest that CBT is more effective than placebo in the treatment of anxiety disorders (116);
- ICBT for SAD is superior to waiting list controls (43, 51, 52, 55, 56, 108);
- only 13-14% recover from SAD without treatment after one year (117), as opposed to 34% who had achieved remission at six-month follow-up in Study I.

In Figure 10, I have also compared the observed pre-post change after ICBT in routine care (Study I) with those reported for several wait-list controls in previous studies; the effect of treatment seems evident.

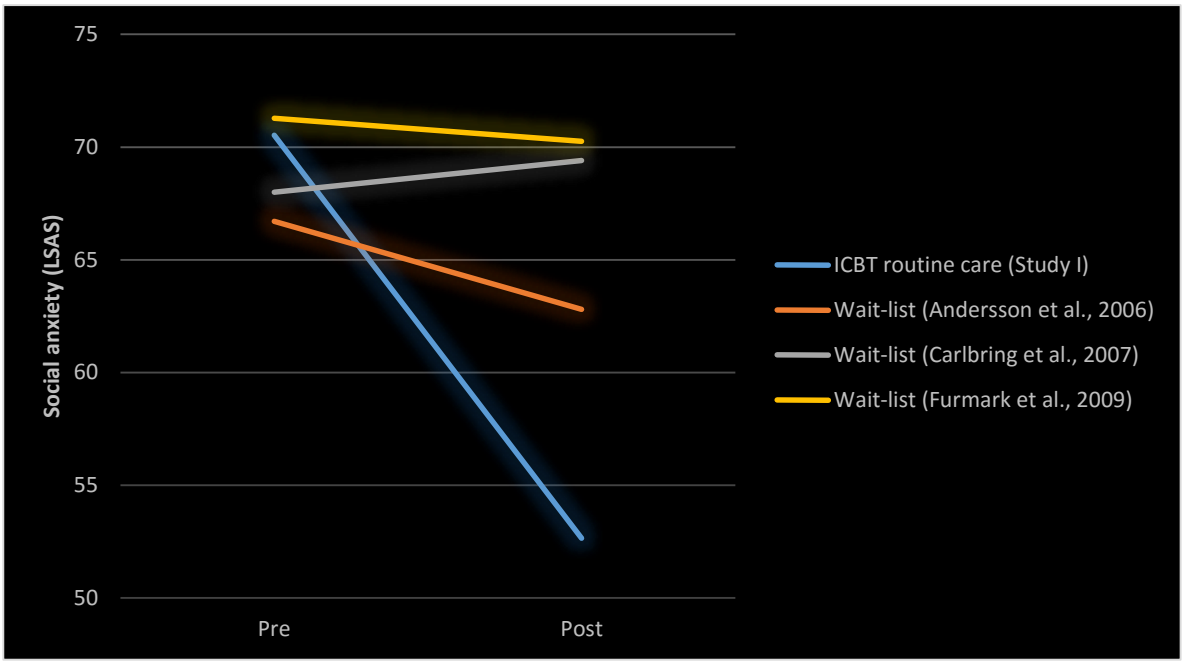

Figure 10. Internet-based cognitive behavioural therapy in routine care compared with wait-list controls. Abbreviations: LSAS, Liebowitz Social Anxiety Scale. References: Andersson G, Carlbring P, Holmstrom A, et al. Internet-based self-help with therapist feedback and in vivo group exposure for social phobia: a randomised controlled trial. *Journal of consulting and clinical psychology* 2006;74:677-86. Carlbring P, Gunnarsdottir M, Hedensjo L, Andersson G, Ekselius L, Furmark T. Treatment of social phobia: randomised trial of internet-delivered cognitive-behavioural therapy with telephone support. *The British journal of psychiatry* 2007;190:123-8. Furmark T, Carlbring P, Hedman E, et al. Guided and unguided self-help for social anxiety disorder: randomised controlled trial. *The British journal of psychiatry* 2009;195:440-7.

4.3.2 Missing data

Attrition is often an issue in observational studies. Hence, there is a risk that the high degree of missing follow-up data in Studies I and II may have led to biased estimates. To address this issue, a number of elaborate NMAR [xiv] analyses were performed in Study I which tested different assumptions of the patterns of missing data and its possible consequences for inferences and estimates. Since results were generally unaffected by these different assumptions, it is unlikely that the observed data loss at follow-up would have significantly affected the outcome estimates. However, all estimates should nonetheless be interpreted with some degree of caution – after all, statistical models are probabilistic, and therefore inherently uncertain.

[xiv] Modelling with data not missing at random.

4.3.3 Possibility of response bias in self-report measures

The reliance on patient-reported outcome measures instead of clinician-rated measures may have increased the risk of possible response bias, thereby affecting the validity of the measurements. To control for this, the correlation between the self-rated and the clinician rated versions of the LSAS was tested to assess their level of agreement. They were found to be highly correlated; $r(572) = .77$, $p < .001$. I therefore believe that the use of self-reports is a valid form of administration. This has also been demonstrated elsewhere (118).

A similar issue might be considered in regard to the cost-effectiveness analyses in Study III, which relied on the self-reported instrument TIC-P for collecting cost data instead of using register data; it is possible that this might have influenced the precision of cost-estimation, since the estimated costs relied on patients' recollections of events on which direct and indirect costs were calculated. On the other hand, just as for the demonstrated correlation between the LSAS and the LSAS-SR, there seems to be a high level of agreement between costs estimated through self-assessments and through registry data (119).

4.3.4 Measurement of adherence and treatment dose received

The ICBT intervention consists of separate modules, similar to sessions in a live CBT intervention. The operational definition of adherence used throughout the studies were the number of *accessed* modules between pre- and post-treatment measurement. However, this estimate does not provide precise information regarding the actual treatment dose received, since we have no quantified measure of the degree to which patients completed each module. However, since this applies to all cases analysed, the relationship between the number of modules and treatment outcome should still be the same.

Another issue concerns the term "adherence" itself. On closer inspection, this term may only tell us about the speed of engaging with the treatment content during a defined period of time (e.g. the 12-week time period of therapist support). If one were to analyse outcome data beyond this timeframe such as in long-term follow-up studies (e.g. Study II), the term "adherence" may be problematic, because, supposing that patients, as they are encouraged to do, continue to engage with the treatment after post-treatment assessment (albeit unguided), the term adherence would no longer be synonymous with the actual treatment dose received, i.e. *in total*.

It is reasonable to assume that individuals differ in their pace of learning and in the ability to assimilate the program material. As was observed in Study II, patients continue to improve after the 12-week mark, which may be indicative of their continued unguided work with the rest of the treatment. Hence, patients that were classified as "non-adherent" in the analyses may in fact have adhered fully if we were to widen the analytic timeframe – they simply might have needed more time to complete the treatment. My reflections in this matter merely concerns the underlying assumption and/or operationalization of treatment adherence as a commonly used term to measure treatment dose, namely that it is limited to a strict timeframe of therapist guidance. An alternative would be to use a term such as "study pace" instead of "adherence",

alluding both to the learning context which ICBT essentially constitutes and to reflect that which is actually measured, namely how much of the treatment was accessed *during a specified period of time*. However, such a term would not be without problems either, because some patients may for example complete the first three modules in three weeks and then drop out, thereby having kept a high pace from one perspective while a low pace from another.

4.3.5 Generalizability

Although the relatively large samples in Studies I, II and IV increases the likelihood of generalizability of observed results, there are limitations as to which populations these may apply to. As for most contemporary research on ICBT, study samples have been predominantly from developed countries such as northwestern Europe and Australia. Consequently, results may not necessarily generalize to global populations. Therefore, future research should aim to replicate these studies in different cultures. As for western populations, the study samples seem to be fairly representative of SAD patients in the general population. For example, when comparing demographic and clinical characteristics with a large national sample of U.S. adults (120), our samples reflects gender differences in prevalence and the age of onset is typically around 15 years of age, which reflect our current sample with a mean age of 33 and a mean time since debut of first SAD symptoms of 16 years.

4.4 FURTHER RESEARCH

4.4.1 Determining optimal resource allocation and utilization

While ICBT is considered as a cost-effective treatment option (mainly because it requires less therapist time on average) determining the most efficient use of therapist resources in the delivery of ICBT is an area that may need more attention, given recent empirical evidence suggesting that also unguided ICBT can be effective for many patients. For example, in Australia, there have been a series of controlled studies testing the efficacy of different versions of guided and unguided ICBT (e.g. adding automated emails and SMS reminders) and different types and degrees of clinician support (44, 55, 56, 107-110). These interventions are highly efficacious in treating SAD, also without therapist guidance. Evidence from independent research groups in Switzerland and in Sweden further add to this body of knowledge confirming the usefulness of ICBT for SAD, both with and without therapist support, demonstrating treatment effects in par with standard treatments (43, 48-53, 59, 60, 111).

Evaluating the clinical effectiveness of unguided treatments for SAD – especially with capabilities of intelligently automated feedback – would therefore be highly interesting, drawing inspiration from the Australian research group having developed and implemented treatment models with such capabilities (107). Since such interventions would further increase the accessibility of effective care, therapist resources providing more individualised support could therefore be allocated more selectively to those who need it the most.

Another approach to study resource utilization may be to evaluate costs and benefits of a standard ICBT clinical pathway from a health care provider's perspective, meaning that a more detailed analysis of the costs and resources needed to deliver care are performed and evaluated against produced health outcomes. Such methods would complement CEAs, which are typically conducted from a societal perspective, by achieving a more concrete understanding of the constituent parts of the whole value chain, from referral to a treated patient. Achieving a detailed map of the overall healthcare processes, its sub-processes and activities as well as observed patient outcomes, calculated resources used and costs accrued may be essential in order to create a system that is capable of continuously monitoring and improving not only the quality of care, but also the *efficiency* of care.

4.4.2 Prevention and early intervention

Due to the early onset of SAD and the risk of chronicity, future research should supplement existing treatments for adults with internet-based interventions that are aimed at children and adolescents. Such early interventions are clearly needed, since approximately 80% of children and adolescents in need of help generally do not receive any treatment (121-124). Low treatment availability is part of the problem, but this group is also highly reluctant to seek help due to stigmatisation and embarrassment, and self-help seems to be the preferred treatment of choice (125). Also, given the high level of computer literacy among today's young generations, the advantages of internet interventions might be even more evident. A recent meta-analysis on ICBT for youth in the treatment of depression and anxiety reported that internet interventions seem to be equally efficacious as face-to-face psychotherapy (126). However, there is limited research on early ICBT interventions for SAD specifically; I am only aware of one ICBT study aimed at youth, and the results were promising with a large pre-post treatment effect size of $d = 0.98$ (111). There are also few studies on using ICBT for prevention – and these are primarily aimed at managing depression (127, 128) – hence this would also be an important area for future research on ICBT for SAD.

4.4.3 Tools for prediction research to increase clinical usability

In Study IV, outcome predictors of ICBT were explored through the use of multilevel modelling. An indication of how different patient and treatment-related characteristics influence the rate of improvement during treatment was achieved. For example, treatment credibility appeared to have a significant relationship with how patients comply with and respond to treatment and a relationship was found between illness severity and the speed of symptomatic change. But how can clinicians use such knowledge in their day-to-day practice? Perhaps what is needed are more instructive decision rules specifically aimed at providing clinical guidance and to facilitate the interpretation of results reported from prediction research studies. A typical situation is when making the decision of either including or excluding patients to ICBT. One possibility would be the use of decision tree analyses. Easily interpretable decision rules and cut-off values would help clinicians make practical use of identified outcome predictors. Clinical decisions could then be based on information regarding

the probability of, for example, remission or treatment response for different subgroups of patients.

4.5 OVERALL CONCLUSIONS OF THE THESIS

This research project has demonstrated that:

- ICBT can be successfully implemented in routine clinical care
- Beneficial effects are maintained
- ICBT is as long-term effective and cost-effective as standard treatment
- ICBT may be suitable also for those with more severe social anxiety
- Adherence predicts improvement
- Treatment credibility is related to improvement and adherence

As an effective and resource-efficient complement to conventional CBT, ICBT may significantly increase access to evidence-based care by overcoming several barriers commonly associated with conventional face-to-face psychotherapy. Consequently, ICBT may contribute to a significant reduction of the societal economic burden of mental illness and provide the public healthcare system with effective means to meet the growing need to manage mental ill-health.

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